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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

| EXAMINER | |
|---|---|
| HUYNH, PHUONG N | |

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| 1644 | 19 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/847,208 | SAXON ET AL. | |
| | Examin r | Art Unit | |
| | Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Thee* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *6/18/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *77-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/18/03 has been entered.

2. Claims 77-95 are pending and are being acted upon in this Office Action.

3. Claim 93 is objected to because "The" should have been "A".

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 77-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated fusion molecule comprising an IgG heavy chain constant region capable of binding to an IgG inhibitory receptor functionally connected to an IgE heavy chain constant region sequence capable of binding to an IgE receptor wherein the fusion protein comprises SEQ ID NO: 7, (2) the said fusion molecular wherein the IgG heavy chain constant region sequence and IgE heavy chain constant region sequence are directly fused, (3) the said fusion molecular wherein the IgG heavy chain constant region sequence and IgE heavy chain constant region sequence are connected via a polypeptide linker of 5 to 25 amino acid residues or 15 to 25 amino acid residues, (4) the said fusion molecular wherein the IgG and IgE heavy chain constant region sequences are from human origin, and said IgG inhibitory receptor and IgE receptor are human, (5) the said fusion molecular wherein the IgG inhibitory receptor is a low affinity FcγRIIb IgG inhibitory receptor, and wherein said IgE receptor is selected from a high-affinity FcεRI receptor and a low-affinity FcεRII receptor (CD23), (6) the said fusion protein wherein the IgG heavy chain constant region is selected from the heavy chain constant regions of IgG1, IgG2, IgG3 and IgG4, (7) the said fusion protein wherein the IgG heavy chain constant region is selected from the heavy chain constant regions of IgG1 heavy chain constant region, (8)

the said fusion protein wherein said IgG1 heavy chain constant region sequence consists of the hinge-CH2CH3 of an IgG1 heavy chain constant region, (9) the said fusion protein wherein said IgG1 heavy chain constant region sequence consists of the hinge-CH2CH3 of an IgG1 heavy chain constant region consists of SEQ ID NO: 3, (10) the isolated fusion molecule comprising an IgG heavy chain constant region capable of binding to an IgG inhibitory receptor functionally connected to an IgE heavy chain constant region sequence capable of binding to an IgE receptor wherein the IgE heavy chain constant region consists of the CH2-CH3-CH4 of a native human IgE heavy chain constant region, (11) the isolated fusion molecule comprising an IgG heavy chain constant region capable of binding to an IgG inhibitory receptor functionally connected to an IgE heavy chain constant region sequence capable of binding to an IgE receptor wherein the IgE heavy chain constant region consists of the CH2-CH3-CH4 of a native human IgE heavy chain constant region consists of SEQ ID ON: 6, (12) the said fusion protein covalently linked to a second identical fusion molecule to form a homodimer, (13) the said fusion protein covalently linked to a second identical fusion molecule to form a homodimer through one or more disulfide bonds, and (14) the fusion molecule of SEQ ID NO: 7 covalently linked to a second identical fusion molecule to form a homodimer, and (15) fusion molecule of SEQ ID NO: 7 covalently linked to a second identical fusion molecule to form a homodimer through one or more disulfide bonds for treating allergy, **does not** reasonably provide enablement for *any* fusion molecule comprising any IgG heavy chain constant region sequence capable of binding to any IgG inhibitory receptor functionally connected to any IgE heavy chain constant region sequence capable of binding to any IgE receptor as set forth in claims 77-95 for preventing *any* allergy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one fusion molecule of SEQ ID NO: 7 consisting of a first polypeptide sequence (SEQ ID NO: 3) which contains a hinge, a CH2 and CH3 domains of the constant region of an IgG1 heavy chain (γhinge--CHγ2-CHγ-3) that binds to a native human low affinity FcγRIIb receptor fused to a second polypeptide of SEQ ID NO: 6 which contains a CH2, CH3 and CH4 domains of the constant region of an IgE heavy chain (CHε2-CHε3-CHε-4) that binds to a native high-affinity IgE receptor FcεRI (See page 24 lines 29-31 bridging page 25 line 1, example on page 53-54 of the specification). The specification further discloses that said first polypeptide and said second polypeptide are linked through a 15 amino acids peptide linker and the resulting fusion molecule can connected to another fusion molecule by interchain disulfide bonds to form a homodimer or heterodimer with two different fusion molecules (See page 26, lines 5-14).

The specification does not teach how to make *any* fusion molecule mentioned above for preventing any allergy because of the following reasons. The specification discloses only one fusion molecule comprising SEQ ID NO: 7. There is insufficient guidance as to the structure of any other fusion molecule. Further, the term "comprising" is open-ended. It expands the fusion molecule to include additional amino acids at either or both ends, in addition to the undisclosed IgG heavy chain constant region sequence capable of binding to any IgG inhibitory receptor and IgE heavy chain constant region sequence capable of binding to any IgE receptor. The specification defines IgG inhibitory receptors are receptors such as various forms of FcγRIIb, gp49b1, p91/PIR-B, LAIR-1, LIR-1 or CD22 (See page 21). There is insufficient guidance as to the amino acid sequence of IgG heavy chain constant region that binds to any FcγRIIb, gp49b1, p91/PIR-B, LAIR-1, LIR-1 or CD22, in turn, the fusion protein is useful for "preventing" allergy. Further, there is no in vivo working example demonstrating that any fusion molecule mentioned above is effective for preventing any allergy.

It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495).

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

As to claim 88, the term "is" is open-ended. It expands the hinge-CH2-CH3 portion of the IgG1 heavy chain constant region to include additional amino acids at either or both ends. There is insufficient guidance as to which undisclosed amino acids to be added and whether the resulting IgG1 heavy chain constant region of the fusion molecule would bind to the IgG inhibitory receptor such as the low affinity FcγRIIb. Further, it is well known that IgE from species such as mouse does not bind to any FcεRI or FcεRII receptor from human. Since the fusion molecule is not enabled, it follows that any fusion molecule covalently linked to a second fusion molecule to form a homodimer through one or more disulfide bonds are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/21/02 and 6/18/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the specification teaches that the CH2-CH3 interface of the IgG Fc domain contains the binding sites for the FcγRIIb IgG inhibitory receptor (page 21, lines 13-15). The specification further teaches that six amino acid residues (Arg-408, Ser-411, Lys-415, Glu-452, Arg-465 and Met-469) of the human IgE heavy chain CH3 domain are involved in binding to the high affinity IgE receptor, FcεRI, and that residues, including His in the C-terminal region of the ε-chain make an important contribution toward the maintenance of high-affinity interaction between IgE and FcεRI.

However, base claim 77 is drawn to an isolated fusion molecule comprising *any* IgG heavy chain constant region sequence capable of binding to *any* IgG inhibitory receptor functionally connected to *any* IgE heavy chain constant region. The specification discloses only one fusion molecule comprising SEQ ID NO: 7. There is insufficient guidance as to the structure of any other fusion molecule. Further, the term "comprising" is open-ended. It expands the fusion molecule to include additional amino acids at either or both ends, in addition to the

undisclosed IgG heavy chain constant region sequence capable of binding to any IgG inhibitory receptor and IgE heavy chain constant region sequence capable of binding to any IgE receptor. The specification defines IgG inhibitory receptors are receptors such as various forms of FcγRIIb, gp49b1, p91/PIR-B, LAIR-1, LIR-1 or CD22 (See page 21). There is insufficient guidance as to the amino acid sequence of IgG heavy chain constant region that binds to any FcγRIIb, gp49b1, p91/PIR-B, LAIR-1, LIR-1 or CD22, in turn, the fusion protein is useful for "preventing" allergy. Further, there is no in vivo working example demonstrating that any fusion molecule mentioned above is effective for preventing any allergy.

6. Claims 77-95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* fusion molecule comprising any IgG heavy chain constant region sequence capable of binding to any IgG inhibitory receptor functionally connected to any IgE heavy chain constant region sequence capable of binding to any IgE receptor as set forth in claims 77-95 for preventing *any* allergy.

The specification discloses only one fusion molecule of SEQ ID NO: 7 consisting of a first polypeptide sequence (SEQ ID NO: 3) which contains a hinge, a CH2 and CH3 domains of the constant region of an IgG1 heavy chain (γhinge--CHγ2-CHγ-3) that binds to a native human low affinity FcγRIIb receptor fused to a second polypeptide of SEQ ID NO: 6 which contains a CH2, CH3 and CH4 domains of the constant region of an IgE heavy chain (CHε2-CHε3-CHε-4) that binds to a native high-affinity IgE receptor FcεRI (See page 24 lines 29-31 bridging page 25 line 1, example on page 53-54 of the specification). The specification further discloses that said first polypeptide and said second polypeptide are linked through a 15 amino acids peptide linker and the resulting fusion molecule can connected to another fusion molecule by interchain disulfide bonds to form a homodimer or heterodimer with two different fusion molecules (See page 26, lines 5-14).

The specification does not teach how to make *any* fusion molecule mentioned above for preventing any allergy because of the following reasons. The specification discloses only one fusion molecule comprising SEQ ID NO: 7. There is insufficient guidance as to the structure of any other fusion molecule. Further, the term "comprising" is open-ended. It expands the fusion

molecule to include additional amino acids at either or both ends, in addition to the undisclosed IgG heavy chain constant region sequence capable of binding to any IgG inhibitory receptor and IgE heavy chain constant region sequence capable of binding to any IgE receptor. The specification defines IgG inhibitory receptors are receptors such as various forms of FcγRIIb, gp49b1, p91/PIR-B, LAIR-1, LIR-1 or CD22 (See page 21). There is insufficient guidance as to the amino acid sequence of IgG heavy chain constant region that binds to any FcγRIIb, gp49b1, p91/PIR-B, LAIR-1, LIR-1 or CD22, in turn, the fusion protein is useful for "preventing" allergy. Further, there is no in vivo working example demonstrating that any fusion molecule mentioned above is effective for preventing any allergy.

With the exception of the specific fusion molecule comprising SEQ ID NO: 7 wherein the specific IgG heavy chain constant region consists of SEQ ID NO: 3 connected to the specific IgE heavy chain constant region sequence consists of SEQ ID NO: 6 for treating allergy, there is inadequate written description about the structure associated with function of any fusion molecule mentioned above because the term "comprising" is open-ended. It expands the fusion molecule to include additional amino acids at either or both ends, in addition to the undisclosed IgG heavy chain constant region sequence capable of binding to any IgG inhibitory receptor and IgE heavy chain constant region sequence capable of binding to any IgE receptor. The specification defines IgG inhibitory receptors are receptors such as various forms of FcγRIIb, gp49b1, p91/PIR-B, LAIR-1, LIR-1 or CD22 (See page 21). There is inadequate written description about which amino acid sequence of which IgG heavy chain constant region that binds to the FcγRIIb, gp49b1, p91/PIR-B, LAIR-1, LIR-1 or CD22, in turn, the fusion protein is useful for "preventing" allergy.

As to claim 88, the term "is" is open-ended. It expands the hinge-CH2-CH3 portion of the IgG1 heavy chain constant region to include additional amino acids at either or both ends. There is inadequate written description about which undisclosed amino acids to be added and whether the resulting IgG1 heavy chain constant region of the fusion molecule would still bind to the IgG inhibitory receptor such as the low affinity FcγRIIb. Given the indefinite number of undisclosed isolated fusion molecule, it follows that any fusion molecule covalently linked to a second fusion molecule to form a homodimer through one or more disulfide bonds are not adequately described. Further, the specification teaches that the CH2-CH3 interface of the IgG Fc domain contains the binding sites for the FcγRIIb IgG inhibitory receptor (page 21, lines 13-15). The specification teaches that six amino acid residues (Arg-408, Ser-411, Lys-415, Glu-452, Arg-465 and Met-469) of the human IgE heavy chain CH3 domain are involved in binding to the

high affinity IgE receptor, FcεRI, and that residues, including His in the C-terminal region of the ε-chain make an important contribution toward the maintenance of high-affinity interaction between IgE and FcεRI. Given the lack of a written description of *any* additional representative species of fusion molecule comprising any IgG functionally connected to any IgE heavy chain constant region, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus for preventing allergy. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/21/02 and 6/18/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the specification teaches that the CH2-CH3 interface of the IgG Fc domain contains the binding sites for the FcγRIIb IgG inhibitory receptor (page 21, lines 13-15). The specification further teaches that six amino acid residues (Arg-408, Ser-411, Lys-415, Glu-452, Arg-465 and Met-469) of the human IgE heavy chain CH3 domain are involved in binding to the high affinity IgE receptor, FcεRI, and that residues, including His in the C-terminal region of the ε-chain make an important contribution toward the maintenance of high-affinity interaction between IgE and FcεRI.

However, the claims are drawn to an isolated fusion molecule comprising *any* IgG heavy chain constant region sequence capable of binding to *any* IgG inhibitory receptor functionally connected to *any* IgE heavy chain constant region. The specification discloses only one fusion molecule comprising SEQ ID NO: 7 from human that binds to human FcγRIIb IgG inhibitory receptor and human IgE receptor. Further, the term "comprising" is open-ended. It expands the fusion molecule to include additional amino acids at either or both ends, in addition to the undisclosed IgG heavy chain constant region sequence capable of binding to any IgG inhibitory receptor and IgE heavy chain constant region sequence capable of binding to any IgE receptor. The specification defines IgG inhibitory receptors are receptors such as various forms of FcγRIIb, gp49b1, p91/PIR-B, LAIR-1, LIR-1 or CD22 (See page 21). There is inadequate written description about which amino acid sequence of which IgG heavy chain constant region that

binds to the FcγRIIb, gp49b1, p91/PIR-B, LAIR-1, LIR-1 or CD22, in turn, the fusion protein is useful for "preventing" allergy.

As to claim 88, the term "is" is open-ended. It expands the hinge-CH2-CH3 portion of the IgG1 heavy chain constant region to include additional amino acids at either or both ends. There is inadequate written description about which undisclosed amino acids to be added and whether the resulting IgG1 heavy chain constant region of the fusion molecule would bind to the IgG inhibitory receptor such as the low affinity FcγRIIb. Given the indefinite number of undisclosed isolated fusion molecule, it follows that any fusion molecule covalently linked to a second fusion molecule to form a homodimer through one or more disulfide bonds are not adequately described. The specification teaches that the CH2-CH3 interface of the IgG Fc domain contains the binding sites for the FcγRIIb IgG inhibitory receptor (page 21, lines 13-15). The specification further teaches that six amino acid residues (Arg-408, Ser-411, Lys-415, Glu-452, Arg-465 and Met-469) of the human IgE heavy chain CH3 domain are involved in binding to the high affinity IgE receptor, FcεRI, and that residues, including His in the C-terminal region of the ε-chain make an important contribution toward the maintenance of high-affinity interaction between IgE and FcεRI. Given the lack of a written description of *any* additional representative species of fusion molecule comprising any IgG functionally connected to any IgE heavy chain constant region, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 77-78, 82-86 and 91-92 are rejected under 35 U.S.C. 102(b) as being anticipated by Presta *et al* (J Biol Chem 269(42): 26368-26373, 1994; PTO 1449).

Presta *et al* teach various isolated fusion molecule such as IgGEL comprising an IgG heavy chain constant region such as human IgG1 residues 291-305, and 329-337 functionally fused to an IgE heavy chain constant regions such as Fcε2-Fcε3 domains (See page 26369,

column 1, in particular) or IgG2/E3 (See page 26370, column 2, last line, in particular). The reference fusion molecule wherein the IgE heavy chain constant region sequence is capable of binding to the IgE receptor such as FcεRI (See abstract, in particular). The reference molecule wherein the IgG heavy chain constant region is inherently capable of binding to any IgG receptor such as the low affinity FcγRIIb inhibitory receptor. Claims 91 and 92 are included in this rejection because the reference fusion molecule inherently capable of forming a homodimer via one or more disulfide bonds since the IgG1 constant region inherently has various cysteine residues. Thus, the reference teachings anticipate the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 77 and 79-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Presta *et al* (J Biol Chem 269(42): 26368-26373, 1994; PTO 1449) in view of WO 88/09344 publication, PTO 1449).

The combined teachings of Presta *et al* have been discussed supra.

The claimed invention in claim 79 differs from the teachings of the reference only that the fusion molecule wherein the IgG heavy chain constant region sequence and IgE heavy chain constant region sequence are connected via a polypeptide linker of 5 to 25 amino acid residues.

The claimed invention in claim 80 differs from the teachings of the reference only that the fusion molecule wherein the IgG heavy chain constant region sequence and IgE heavy chain

constant region sequence are connected via a polypeptide linker consists of 10 to 25 amino acid residues.

The claimed invention in claim 81 differs from the teachings of the reference only that the fusion molecule wherein the IgG heavy chain constant region sequence and IgE heavy chain constant region sequence are connected via a polypeptide linker consists of 15 to 25 amino acid residues.

The WO 88/09344 publication teaches various polypeptide linkers such Gly-Gly-Gly-Gly-Ser which is at least 5 amino acid residues that can be link in tandem to form (Gly-Gly-Gly-Gly-Ser)3 which is at least 15 amino acid residues or it can be link to form (Gly4-Ser)5, which is at least 20 amino acid residues. The reference polypeptide linker is designed so as to exhibit little propensity for secondary structure and not to interfere with domain folding when connecting the $V_H$ carboxy-and $V_L$ amino-termini which is the variable heavy and light chain of the immunoglobulin (See page 52, 1st paragraph, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to link any IgG heavy chain constant region sequence and IgE heavy chain constant region sequence as taught by Presta *et al* using the polypeptide linker as taught by the WO 88/01737 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 88/01737 teaches that the reference polypeptide linker is designed so as to exhibit little propensity for secondary structure and not to interfere with domain folding when connecting the $V_H$ carboxy-and $V_L$ amino-termini which is the variable heavy and light chain of the immunoglobulin (See page 52, 1st paragraph, in particular).

12. Claims 77-78, 82-89 and 91-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,336,603 (of record, Aug 1994, PTO 892) in view of WO 95/14779 (June 1995, PTO 892), Basu *et al* (of record, J Biol Chem 268(18): 13118-27, June 1993; PTO 892) and Daeron *et al* (J Clin Invest 95(2): 577-85, Feb 1995; PTO 892).

The '603 patent teaches a fusion molecule such as CD4-IgG comprising a human IgG1 constant region such as $IgG_1$, that is capable of binding to a native IgG receptor such as the FcγRIIb functionally connected to CD4 (See column 3, Summary, in particular). The '603 patent

further teaches the CD4 molecule is fused to the Fc portion of IgG1 wherein the Fc portion of IgG1 comprises at least the functionally active hinge, CH2 and CH3 domains of an immunoglobulin heavy chain (See column 5, lines 61-67, in particular). Claim 88 is included in this rejection because the term "is" is open ended. It expands the claimed hinge-CH2CH3 portion of any IgG1 heavy chain constant to include additional amino acids at either or both ends to read on the reference IgG1 constant region. The '603 patent teaches that any fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular).

The claimed invention as recited in claim 77 differs from the teachings of the reference only that the fusion molecule comprises an IgG heavy chain constant region sequence functionally connected to an IgE heavy chain constant regions capable of binding to an IgE receptor.

The claimed invention as recited in claim 82 differs from the teachings of the reference only that the fusion molecule wherein the IgG and IgE heavy chain constant region sequences are of human origin and said IgG inhibitory receptor and IgE receptor are human.

The claimed invention as recited in claim 91 differs from the teachings of the reference only that the fusion molecule covalently linked to a second identical fusion molecule to form a homodimer.

The claimed invention as recited in claim 92 differs from the teachings of the reference only that the fusion molecule covalently linked to a second identical fusion molecule to form a homodimer wherein the linkage is through one or more disulfide bonds.

The WO 95/14779 publication teaches human IgE Fc (hIgE-Fc) comprising the second, third and fourth constant region domains (Cε2-Cε4) (See page 1, second full paragraph, Abstract, Figure 1, in particular), which are useful in the treatment of allergy conditions (See page 5, first paragraph, in particular). The WO 95/14779 publication further teaches that the reference hIgE Fc has two Cys 241 and Cys 328 in parallel to form homodimer through interchain disulfide bond (See page 15, lines 1-3, Figure 1, in particular).

Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains that are sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE can block the release of histamine from cells expressing human Fc epsilon RI. Basu *et al* further teach the Fc region of

IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains containing the Cys328 residue which can form interchain disulfide (S-S) bonds (See abstract, in particular).

Daeron *et al* teach that IgE induced mediator release is inhibited by crosslinking FcεRI to FcγRIIb1 or FcγRIIb1 which are low affinity receptors and is useful for desensitization in allergic patients (See page 577, column 1, page 579, column 2, Figures 3a-3b, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the CD4 molecule as taught by the '603 patent for the human IgE heavy chain constant region that binds to an IgE receptor as taught by the WO 95/14779 publication or Basu *et al* for a fusion molecule comprising the IgG heavy chain constant region that capable of binding to IgG inhibitory receptor such as low affinity FcγRIIb fused to an IgE heavy chain constant region sequence that is capable of binding to an IgE receptor such as high affinity receptor (Fc epsilon RI) or low affinity receptor (Fc epsilon RII) as taught by the '603 patent, the WO 95/14779 publication and Basu *et al* to inhibit IgE induced mediator release. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Daeron *et al* teach that IgE induced mediator release is inhibited by crosslinking FcεRI to FcγRIIb1 or FcγRIIb1 which are low affinity receptors and is useful for desensitization in allergic patients (See page 577, column 1, page 579, column 2, Figures 3a-3b, in particular). The WO 95/14779 publication teaches human IgE Fc (hIgE-Fc) comprising the second, third and fourth constant region domains (Cε2-Cε4) (See page 1, second full paragraph, Abstract, Figure 1, in particular), which are useful in the treatment of allergy conditions (See page 5, first paragraph, in particular). Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains is sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE which can block the release of histamine from cells expressing human Fc epsilon RI. The '603 patent teaches fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular).

Applicants' arguments filed 11/21/02 and 6/18/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) there is no motivation either explicit or implied can be discerned from the references to make such combination to arrive at the fusion molecule of the

present invention, (2) even if the cited references could be properly combined, the Examiner failed to make a prima facie showing that their combination would make obvious the invention claimed. The claimed invention is direct to fusion molecules that are capable of crosslinking an IgG inhibitory receptor with an IgE receptor (e.g. FcεRI). While the cited references establish that similar antibody-like structures immunoadhesins were known in the art at the time the present invention was made they provide no expectation that the fusion molecules of the present invention would possess valuable properties enabling their use in allergy therapy. (3) The structure and function of the fusion molecules of the present invention have been recognized by those skilled in the art as unexpected, and worthy of publication in a prestigious peer-reviewed scientific journal.

However, the '603 patent teaches that any fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular). Daeron *et al* teach that IgE induced mediator release is inhibited by crosslinking FcεRI to FcγRIIb1 or FcγRIIb1 which are low affinity receptors and is useful for desensitization in allergic patients (See page 577, column 1, page 579, column 2, Figures 3a-3b, in particular). Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains that are sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE can block the release of histamine from cells expressing human Fc epsilon RI. The WO 95/14779 publication teaches human IgE Fc (hIgE-Fc) comprising the second, third and fourth constant region domains (Cε2-Cε4) (See page 1, second full paragraph, Abstract, Figure 1, in particular), which are useful in the treatment of allergy conditions (See page 5, first paragraph, in particular).

In response to Applicants' argument that even if the cited references could be properly combined, the Examiner failed to make a prima facie showing that their combination would make obvious the invention claimed since the claimed invention is direct to fusion molecules which are capable of crosslinking an IgG inhibitory receptor with an IgE receptor (e.g. FcεRI), Daeron *et al* teach that IgE induced mediator release is inhibited by crosslinking FcεRI to FcγRIIb1 or FcγRIIb1 which are low affinity receptors and is useful for desensitization in allergic patients (See page 577, column 1, page 579, column 2, Figures 3a-3b, in particular).

13. Claims 79-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,336,603 (of record, Aug 1994, PTO 892) in view of WO 95/14779 publication (June 1995, PTO 892), Basu *et al* (of record, J Biol Chem 268(18): 13118-27, June 1993; PTO 892) and Daeron *et al* (J Clin Invest 95(2): 577-85, Feb 1995; PTO 892) as applied to claims 77-78, 82-89 and 91-92 mentioned above and further in view of WO 88/09344 publication, PTO 1449).

The combined teachings of the '603 patent, WO 95/14779 publication, Basu *et al* and Daeron *et al* have been discussed supra.

The claimed invention in claim 79 differs from the teachings of the references only that the fusion molecule wherein the IgG heavy chain constant region sequence and IgE heavy chain constant region sequence are connected via a polypeptide linker of 5 to 25 amino acid residues.

The claimed invention in claim 80 differs from the teachings of the references only that the fusion molecule wherein the IgG heavy chain constant region sequence and IgE heavy chain constant region sequence are connected via a polypeptide linker consists of 10 to 25 amino acid residues.

The claimed invention in claim 81 differs from the teachings of the references only that the fusion molecule wherein the IgG heavy chain constant region sequence and IgE heavy chain constant region sequence are connected via a polypeptide linker consists of 15 to 25 amino acid residues.

The WO 88/09344 publication teaches various polypeptide linker such Gly-Gly-Gly-Gly-Ser which is at least 5 amino acid residues that can be link in tandem to form (Gly-Gly-Gly-Gly-Ser)3 which is at least 15 amino acid residues or can be link to form (Gly4-Ser)5 which is at least 20 amino acid residues. The reference polypeptide linker is useful because it exhibits little propensity for secondary structure and would not to interfere with domain folding when connecting the $V_H$ carboxy-and $V_L$ amino-termini which is the variable heavy and light chain of the immunoglobulin (See page 52, 1st paragraph, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to link any IgG heavy chain constant region sequence and IgE heavy chain constant region sequence as taught by the '603 patent, WO 95/14779 publication, Basu *et al* and Daeron *et al* using the polypeptide linker as taught by the WO 88/01737 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 88/01737 teaches that the reference polypeptide linker is designed so as to exhibit little propensity for secondary structure and not to interfere with domain folding when connecting the $V_H$ carboxy-and $V_L$ amino-termini which is the variable heavy and light chain of the immunoglobulin (See page 52, 1st paragraph, in particular).

Applicants' arguments filed 11/21/02 and 6/18/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) there is no motivation either explicit or implied can be discerned from the references to make such combination to arrive at the fusion molecule of the present invention, (2) even if the cited references could be properly combined, the Examiner failed to make a prima facie showing that their combination would make obvious the invention claimed. The claimed invention is direct to fusion molecules, which are capable of crosslinking an IgG inhibitory receptor with an IgE receptor (e.g. FcεRI). While the cited references establish that similar antibody-like structures immunoadhesins were known in the art at the time the present invention was made they provide no expectation that the fusion molecules of the present invention would possess valuable properties enabling their use in allergy therapy. (3) The structure and function of the fusion molecules of the present invention have been recognized by those skilled in the art as unexpected, and worthy of publication in a prestigious peer-reviewed scientific journal.

However, the '603 patent teaches that any fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular). Daeron *et al* teach that IgE induced mediator release is inhibited by crosslinking FcεRI to FcγRIIb1 or FcγRIIb1 which are low affinity receptors and is useful for desensitization in allergic patients (See page 577, column 1, page 579, column 2, Figures 3a-3b, in particular). Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains that are sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE can block the release of histamine from cells expressing human Fc epsilon RI. The WO 95/14779 publication teaches human IgE Fc (hIgE-Fc) comprising the second, third and fourth constant region domains (Cε2-Cε4) (See page 1, second full paragraph, Abstract, Figure 1, in particular), which are useful in the treatment of allergy conditions (See page 5, first paragraph, in particular).

In response to Applicants' argument that even if the cited references could be properly combined, the Examiner failed to make a prima facie showing that their combination would make obvious the invention claimed since the claimed invention is direct to fusion molecules which are capable of crosslinking an IgG inhibitory receptor with an IgE receptor (e.g. FcεRI). However, Daeron *et al* teach that IgE induced mediator release is inhibited by crosslinking FcεRI to FcγRIIb1 or FcγRIIb1 which are low affinity receptors and is useful for desensitization in allergic patients (See page 577, column 1, page 579, column 2, Figures 3a-3b, in particular).

14. Claim 85 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,336,603 (of record, Aug 1994, PTO 892) in view of WO 95/14779 publication (June 1995, PTO 892), Basu *et al* (of record, J Biol Chem 268(18): 13118-27, June 1993; PTO 892) and Daeron *et al* (J Clin Invest 95(2): 577-85, Feb 1995; PTO 892) as applied to claims 77-78, 82-89 and 91-92 mentioned above and further in view of US Pat No. 5,925,351 (of record, Jul 1999, PTO 892).

The combined teachings of the '603 patent, WO 95/14779 publication, Basu *et al* and Daeron *et al* have been discussed supra.

The claimed invention in claim 85 differs from the teachings of the references only that the fusion molecule wherein the IgG heavy chain constant region is selected from the heavy chain constant regions of IgG2, IgG3 and IgG4.

The '351 patent teaches fusion molecule (LT-β-R-Fc) comprising a first polypeptide of LT-β-R functionally connected to the human Fc domains of various IgG such as IgG1, IgG2, IgG3 and IgG4 based on the desirable secondary effector functions for the particular immune response such as Fc domain of IgG1 is advantageous to harm or kill LT-bearing target cell, or IgG4 Fc domain if it desirable for binding of fusion molecule without triggering the complement system (See column 12 lines 58-67 bridging column 13, lines 1-4, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the Fc domains of IgG1 as taught by the '603 patent with the Fc domains of various IgG such as IgG2, IgG3 or IgG4 as taught by the '351 patent for a fusion molecule comprising the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains as taught by the WO 95/14779 publication or Basu *et al* functionally connected to the various Fc domains of IgG1, IgG2, IgG3 or IgG4 as taught by the '603 patent and the '351 patent to crosslink FcεRI to FcγRIIb1 or FcγRIIb1 as taught by Daeron *et al* that inhibit IgE induced mediator release (See page 577, column 1, page 579, column 2, Figures 3a-3b, in particular).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '351 patent teaches that one can select a Fc domain based on the desirable secondary effector functions for the particular immune response such as Fc domain of IgG1 is advantageous to harm or kill LT-bearing target cell, or IgG4 Fc domain if it desirable for binding of fusion molecule without triggering the complement system (See column 12 lines 58-67 bridging column 13, lines 1-4, in particular). The '603 patent teaches fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular). Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains is sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE which can block the release of histamine from cells expressing human Fc epsilon RI. Daeron *et al* teach that IgE induced mediator release is inhibited by crosslinking FcεRI to FcγRIIb1 or FcγRIIb1 which are low affinity receptors and is useful for desensitization in allergic patients (See page 577, column 1, page 579, column 2, Figures 3a-3b, in particular).

Applicants' arguments filed 11/21/02 and 6/18/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) there is no motivation either explicit or implied can be discerned from the references to make such combination to arrive at the fusion molecule of the present invention, (2) even if the cited references could be properly combined, the Examiner failed to make a prima facie showing that their combination would make obvious the invention claimed. The claimed invention is direct to fusion molecules that are capable of crosslinking an IgG inhibitory receptor with an IgE receptor (e.g. FcεRI). While the cited references establish that similar antibody-like structures immunoadhesins were known in the art at the time the present invention was made they provide no expectation that the fusion molecules of the present invention would possess valuable properties enabling their use in allergy therapy. (3) The structure and function of the fusion molecules of the present invention have been recognized by those skilled in the art as unexpected, and worthy of publication in a prestigious peer-reviewed scientific journal.

However, the '603 patent teaches that any fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular).

Daeron *et al* teach that IgE induced mediator release is inhibited by crosslinking FcεRI to FcγRIIb1 or FcγRIIb1 which are low affinity receptors and is useful for desensitization in allergic patients (See page 577, column 1, page 579, column 2, Figures 3a-3b, in particular). Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains that are sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE can block the release of histamine from cells expressing human Fc epsilon RI. The WO 95/14779 publication teaches human IgE Fc (hIgE-Fc) comprising the second, third and fourth constant region domains (Cε2-Cε4) (See page 1, second full paragraph, Abstract, Figure 1, in particular), which are useful in the treatment of allergy conditions (See page 5, first paragraph, in particular).

In response to Applicants' argument that even if the cited references could be properly combined, the Examiner failed to make a prima facie showing that their combination would make obvious the invention claimed since the claimed invention is direct to fusion molecules which are capable of crosslinking an IgG inhibitory receptor with an IgE receptor (e.g. FcεRI), Daeron *et al* teach that IgE induced mediator release is inhibited by crosslinking FcεRI to FcγRIIb1 or FcγRIIb1 which are low affinity receptors and is useful for desensitization in allergic patients (See page 577, column 1, page 579, column 2, Figures 3a-3b, in particular).

15. Claims 90 and 93-95 are free of prior art.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

18. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401. The IFW official Fax number is (703) 872-9306. For After Final, the Fax number is (703) 872-9307.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
August 25, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600